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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/520,901	04/13/2005	Toshiyoshi Fujiwara	09857/0202272-US0	2780

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EXAMINER	
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ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/520,901	FUJIWARA ET AL.	
	Examiner	Art Unit	
	WU-CHENG Winston SHEN	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 October 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 January 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/17/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim amendments filed on Oct 17, 2008 have been received and entered. Claims 1-3 are cancelled. Claim 12 is newly added. Claims 4-12 are pending and currently under examination.

The Declaration filed by Toshiyoshi Fujiwara on 10/17/2008 has been considered.

This application 10/520,501 is a 371 of PCT/JP03/08573 filed on 07/07/2003, and claims the benefits of foreign application JAPAN 2002-198941 07/08/2002.

Claim Rejection - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. Claims 4-8 and 11 remain rejected and newly added claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over **Morin et al.** (Morin et al., 2000, WO 00/46355, international publication date, August 10, 2000; this reference is disclosed in IDS filed on 04/25/2006, listed as reference No. BA) in view of **Li et al.** (Li et al., A hepatocellular carcinoma-specific adenovirus variant, CV890, eliminates distant human liver tumors in combination with doxorubicin. *Cancer Res.* 61(17): 6428-36, 2001; this reference is disclosed in IDS filed on 04/25/2006, listed as reference CC). Applicant's arguments filed 10/17/2008 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 12-14 of the Non-Final office action mailed on 06/19/07, and further

elaborated on pages 5-8 of the office action mailed on 06/20/2008. *The inclusion of claim 12 in this rejection is necessitated by claim amendments filed by Applicant on 10/17/2008 adding new claim 12.*

Claim interpretation: Newly added claim 12 reads as follows: The recombinant virus according to claim 5, wherein replication of the virus kills the cancer cell. The limitation "wherein replication of the virus kills the cancer cell" is considered as inherent properties of the recited recombinant virus because the structure of the recombinant virus remains the same.

As set forth at pages 12-14 of the Non-Final office action mailed on 06/19/06, Morin et al., 2000 disclosed use of the hTERT promoter to selectively direct expression in cancer cells. More specifically, Morin et al., 2000 taught oncolytic viruses, in which a toxin or a genetic element essential for viral replication is placed under control of the TERT promoter. Thereby, the virus that replicates preferentially in cells expressing TERT, and thereby selectively lyses cancer cells (See *in vitro* Example 4 on transfected human cell lines, pages 35-36, and *in situ* Example 3 on transplanted human tumor 143B cells on nude mice, page 35, Morin et al., 2000).

While Morin et al. do not teach an adenovirus with IRES inserted between E1A and E1B in an adenovirus as recited in claim 4 of instant application, operably linked to the hTERT promoter, Li taught an adenoviral construct comprising promoter AFP (α-Fetoprotein, a hepatocyte specific promoter) operably linked to E1A-IRES-E1B to cause efficient replication and destruction of hepatocarcinoma cells.

Therefore, it would have been obvious to combine the teachings of Morin et al., with the teachings of Li et al. to arrive at the claimed vector and methods for killing cancer cells.

The essence of ***Applicant's arguments*** filed on 10/17/2008 is essentially the same as that of Applicant's arguments filed 01/14/2008. The Examiner's ***Response to Applicant's arguments*** is revised and summarized below.

Applicant argues that none of the cited references disclose or suggest the hTERT promoter for driving expression of E1A-IRES-E1B construct as recited in claim 4 and from which claims 5-12 depend (See page 6 of Remark filed on 10/17/2008), and Morin does not teach or suggest, or provide any indication for the success for the combination of hTERT with any other construct, much less the E1A-IRES-E1B construct to broadly replicate in cancer cell (See page 7 of Remark filed on 10/17/2008).

In response, Morin is relied upon for teaching selective tumor cell expression using the hTERT promoter whereas Li is relied on for teachings E1A-IRES-E1B expression cassette. A promoter can drive an exogenous downstream expression cassette is well known in the art and the swapping between promoters for expressing a given cassette is a common practice in the art with a reasonable expectation of success. In instant case, the claimed recombinant virus only requires an exchange of AFP promoter (α-Fetoprotein, a hepatocyte specific promoter) with a hTERT promoter (a cancer cell specific promoter) to arrive at the intended use of the viral vector in killing various cancer cells, rather than limited to hepatic cancer cells.

2. Claims 4, 5, 8, 9, and 10 remain rejected under 35 U.S.C. 103(a) as being unpatentable over **Morin et al.** (Morin et al., 2000, WO 00/46355, international publication date, August 10, 2000; this reference is disclosed in IDS filed on 04/25/2006, listed as reference No. BA) in view of **Li et al.** (Li et al., A hepatocellular carcinoma-specific adenovirus variant, CV890, eliminates

distant human liver tumors in combination with doxorubicin. *Cancer Res.* 61(17): 6428-36, 2001; this reference is disclosed in IDS filed on 04/25/2006, listed as reference CC) as applied to claims 1-8 and 10 above, and further in view of **Cheng et al.** (Cheng et al., U.S. patent application No. 2003/0104625, publication date, June 5, 2003; filed Feb. 22, 2002; this reference is cited in the office action dated 06/19/2007). Applicant's arguments filed 10/17/2008 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 8-10 of the Non-Final office action mailed on mailed on 06/20/2008.

For the clarity and completeness of this office action, the rejection for the reasons of record advanced on pages 8-10 of the Non-Final office action mailed on mailed on 06/20/2008, is documented below.

The teachings Morin et al. and Li et al. have been discussed in the preceding section of the rejection of claims 1-8 and 10 under 35 U.S.C. 103(a) as being unpatentable over Morin et al. in view of Li et al.

None of Morin et al. and Li et al. teaches various cancer recited in claim 9 and ostesarcoma and brain tumor recited in claim 10 of instant application.

However, at the time of filing of instant application, treating a type of cancer cell *in vitro* using adenovirus as an anticancer agent (claims 9 and 10 of instant applicant) was known in the art. For instant, Cheng et al. teach tumor and normal tissues, including liver, kidney, lung, bone marrow, brain, spleen, and ovary, were collected from various experimental mice groups, which was administered with adenoviral vector (See paragraph [0570], Cheng et al., 2003).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to incorporate the teachings of Cheng et al. regarding treating various cancer cells using adenovirus as an anticancer with the combined teachings of Morin et al. and Li et al. regarding administration of polynucleotide comprising E1A-IRES-E1B cassette expressed under the control of hTERT promoter for lysis of cancer cells to arrive at the method of killing brain cancer cells *in vitro* comprising the step of administering recombinant virus comprising polynucleotide E1A-IRES-E1B cassette expressed via the control of hTERT promoter, as recited in claims 9 and 10 of instant application.

One having ordinary skill in the art would have been motivated to incorporate the teachings of Cheng et al. regarding treating various cancer cells with adenovirus with the combined teachings of Morin et al. and Li et al. regarding administration of polynucleotide comprising E1A-IRES-E1B cassette expressed via the control of hTERT promoter for killing cancer cells because Morin et al teaches the activity of hTERT promoter is highly specific for cancer cells, which includes brain cancer cells taught by Change et al.

There would have been a reasonable expectation of success given (i) successful demonstration of expression of E1A-IRES-E1B cassette under both transcriptional control of human TERT promoter, by the teachings of Morin et al, and translational control, by the teachings of Li et al for killing cancer cells, and (ii) the demonstration of hTERT promoter control the transcription of adenovirus E4 gene by Cheng et al. (See Figure 49, Change et al.)

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Applicant's arguments and ***Response to applicant's arguments***

(i) Applicant argues that in contrast to the Examiner's conclusion relating to the combination of Li, Morin, and further in combination with Cheng, a skilled artisan would have understood that the expression of E1B gene under the control of IRES sequence would not be at a sufficient level to cause tumor cell lysis via viral replication. Applicant argues that even if a skilled artisan reading Morin decided to control the expression of E1B at the translational level, there would have been no reasonable expectation that the arrangement of IRES sequence upstream of E 1B gene would successfully control the expression of E1B gene at a level sufficient to cause tumor cell lysis by viral replication. Therefore, there would have also been no expectation of success or motivation to combine any of these elements described Li, Morin, or Cheng as alleged by the Examiner (See pages 8-10 of Remark filed on 10/17/2008).

In response, as responded in the maintained rejection of claims 4-8, 11, and 12 under 35 U.S.C. 103(a) as being unpatentable over Morin et al. in view of Li et al., Morin is relied upon for teaching selective tumor cell expression using the hTERT promoter whereas Li is relied on for teachings E1A-IRES-E1B expression cassette. It is emphasized again that Li teaches the same **E1A-IRES-E1B** expression cassette as claimed in instant application, not three separated pieces of DNA as Applicant argues. Cheng et al is relied upon for teaching specific tumors recited in claims 9 and 10. Li et al. has clearly demonstrated that E1A-IRES-E1B expression cassette under the control of AFP promoter (α-Fetoprotein, a hepatocyte specific promoter) functions in hepatic cancer. Furthermore, Cheng et al further demonstrates that hTERT promoter controls the transcription of adenovirus E4 gene in the context of oncolytic adenoviral vectors (See abstract and Figure 49, Change et al.). The Examiner maintains the position that there

would have been a reasonable expectation of success to arrive at the claimed invention given the combined teachings of Morin et al. Li et al., and Cheng et al.

Applicant's arguments pertaining to the improvements and advantages of claimed cassette, adenoviral constructs, and methods (See page 10 of Remark filed on 10/17/2008) have been fully considered and found not persuasive. It is emphasized that the intended use of the products (claims 4-7 and 12) bears limited, if any, patentable weight, and the claimed methods (claims 8-11) as written only require an active step of administering the claimed recombinant viral vector, which leads to the killing a of any given cancer cell either *in vitro* or *in vivo*. The clinical data disclosed in the Declaration filed by Toshiyoshi Fujiwara on 10/17/2008 appears to be more relevant to the previous withdrawn enablement rejection. The Declaration does not provide any evidence that renders the claims as written non-obvious or could not be practiced without a reasonable expectation of success.

(ii) Applicant argues the claimed invention is non-obvious because of secondary considerations pertaining to commercial success of Telomelysin® (OBP-301), which contains the polynucleotide construct of claim 4 and is a viral construct encompassed by claim 5 (See page 11 of Remark filed on 10/17/2008).

In response, it is noted that increase in the sale of a given product in a market is determined by multiple factors, including marketing strategy, business methods for selling the product, increase in the demand etc. There is no evidence on the record, the asserted commercial success of Telomelysin® (OBP-301) has anything to do with the asserted non-obvious of the products and methods claimed in instant application. In particular, MPEP §716.03 states that Applicants bear the burden of proof for establishing a nexus between the claimed invention and

commercial success. The Federal Circuit has acknowledged that applicant bears the burden of establishing nexus, stating:

> In the *ex parte* process of examining a patent application, however, the PTO lacks the means or resources to gather evidence which supports or refutes the applicant's assertion that the sale constitutes commercial success. *C.f. Ex parte Remark*, 15 USPQ2d 1498, 1503 (Bd. Pat. App. & Int. 1990) (evidentiary routine of shifting burdens in civil proceedings inappropriate in *ex parte* prosecution proceedings because examiner has no available means for adducing evidence). Consequently, the PTO must rely upon the applicant to provide hard evidence of commercial success.

In the instant case, Applicants have provided an Exhibit that shows a license agreement and a press release speculating financial terms of the agreement, but no hard evidence of commercial success.

(iii) Applicant argues the claimed invention is non-obvious because of secondary considerations pertaining to failure of others and long felt unsolved need. Applicant cites two publications (Rodriguez et al., *Cancer Res.*, 57:2559- 2563, 1997; and Kurihara et al., *J. Clin. Investig.*, 106:763-771, 2000) that describe the targeting and other problems associated with adenoviral constructs. Applicant states that **Rodriguez et al.** describes adenoviral constructs selective for antigen-positive prostate cancer cells, and **Kurihara et al.** describes adenoviral constructs selective for human breast carcinoma cells expressing the MUC1 antigen. Applicant argues that while these constructs target specific cancers, they do not exhibit the broad selective targeting for other types of tumors as demonstrated by the results using the claimed constructs (See page 12 of Remark filed on 10/17/2008).

In response, it is unclear to the Examiner what exactly the long-felt unsolved need is met by claimed invention but failed by Rodriguez et al. and Kurihara et al. MPEP §716.04 shows that applicants must establish that a long-felt need requires objective evidence that an art

recognized problem existed for a long period of time without solution by others, that it must not have been satisfied by another before the invention by applicants, and that the instant invention must satisfy the long-felt need. In particular, a long-felt need should be analyzed as of the date the problem is identified and articulated and there is evidence of efforts to solve that problem. Cancer research has been ongoing for decades, and to the best of Examiner's knowledge on cancer research, selective killing of cancer cells without harming non-cancer cells have been the ultimate goal, i.e. the long-felt need for effective therapeutic cancer treatment. What Rodriguez et al. (replication competent adenovirus targeting prostate cancer cells) and Kurihara et al. (replication competent adenovirus targeting breast cancer cells) accomplished is exactly steps moving forward to this goal, despite differences in targeting mechanisms. There is no evidence on the record that the asserted "broad selective targeting for other types of tumors as demonstrated by the results using the claimed constructs" is considered as long-felt unsolved need in the field of cancer research. To the best of Examiner's understanding of the status of art relevant to the claimed invention, "broad selective targeting" refers to oncolytic adenoviruses that can selectively replicate in cancer cells and lead to the lysis of cancer cells (i.e. broadly reads on lysis of any cancer cells that propagate faster than normal cells). However, oncolytic adenoviruses are well known in art at the time of filing of instant application, including Morin et al. and Cheng et al. cited in the maintained 103 rejections in this office action. Applicant should clarify what exactly the long-felt unsolved need is met by claimed invention but failed skilled artisan in the filed of cancer research. For art rejections, Applicant is reminded again that the intended use of the products (claims 4-7 and 12) bears limited, if any, patentable weight, and the claimed methods (claims 8-11) as written only require an active step of

administering the claimed recombinant viral vector, which leads to the killing a of any given cancer cell either *in vitro* or *in vivo*.

Conclusion

3. No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, Jr. can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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